

**PATENT
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APPLICATION FOR UNITED STATES LETTERS PATENT

For

**PHARMACEUTICAL DOSAGE FORM BEARING
PREGNANCY-FRIENDLY INDICIA**

by

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TITLE OF THE INVENTION

Pharmaceutical dosage form bearing pregnancy-friendly indicia

FIELD OF THE INVENTION

[0001] The present invention relates to pharmaceutical dosage forms

5 intended for use during pregnancy.

BACKGROUND OF THE INVENTION

[0002] During pregnancy a variety of medical conditions require treatment

with therapeutic agents. For instance, in Canada, excessive nausea and vomiting, possibly leading to hyperemesis gravidarum, are routinely treated with the
10 prescription drug Diclectin® which contains a mixture in equal amounts of two active ingredients, namely pyridoxine HCl and doxylamine succinate.

[0003] Other conditions, pre-existing or developed during pregnancy, for example: diabetes, hypertension, blood clots, depressive illness and heart disease are also commonly treated with prescription drugs.

15 [0004] In the case of pre-existing medical conditions numerous studies

have shown that women have a tendency to abruptly stop taking their medications upon learning of the pregnancy, due to the perceived fear of birth defects¹. In many cases, the risk to the health of the expectant mother and her baby is much higher if she stops or reduces her treatment than if she keeps taking the required
20 medications.

[0005] Because of this perceived risk of harm to the fetus, otherwise known as the teratogenic risk, it is common for expectant mothers to discontinue taking a prescribed drug or to voluntarily diminish the prescribed dosage regimen. This often leads to dosage levels below therapeutic ranges in turn leading patients and

the medical community to incorrectly conclude that a particular drug is clinically ineffective.

5 [0006] Discontinuing or altering drug therapy, often against competent medical prescription, may have grave consequences indeed. The health of the expectant mother and vicariously of the fetus may be put at great risk because of poor compliance with competent medical prescription. In many instances, the teratogenic risks must be weighed against the risk of catastrophic illness or worsening condition on the part of the expectant mother.

10 [0007] Even discounting the particular problem of patient compliance during pregnancy, drug therapy patient compliance is a widespread and difficult problem in the medical community. Non-compliance with prescribed drug dosage regimen is a huge health problem for patients in general. For example, it is estimated that less than 25% of outpatients will complete a 10 day course of antibiotic therapy for a strep throat or otitis media.

15 [0008] Matsui² described that non-compliance with prescribed medication regimens may take many forms, including failure to fill the prescription, incorrect dosage, improper dosing interval, and premature discontinuation of the drug. Of course, the problem of non-compliance is magnified during pregnancy due to the importance of fetal safety.³

20 [0009] Whenever women delay or discontinue use of medications during pregnancy due to fears related to fetal safety, the result may be a worsening of the condition and hospitalisation with use of multiple drug therapy. Furthermore, depending on the underlying condition, the worsening of the condition has serious consequences even including suicidal ideation. Einarson showed in her study¹ on abrupt discontinuation of psychotropic drugs during pregnancy due to teratogenic fears, that 70.3% of women reported physical and psychological adverse effects to

the point that 29.7% reported suicidal ideation (one third of them were hospitalised).

- [0010] Despite these appalling statistics, the perception of the expectant mother remains shrouded by well-known errors of the past such as the widely publicized cases of thalidomide-induced fetal malformations. The graphic evidence of birth defects attributed to Thalidomide exposure during early pregnancy has left a teratogenicity stigma on all medications. Hence, it is commonly thought that all medications are to be avoided during pregnancy. In the study entitled "*Prevention of Unnecessary Pregnancy Terminations by Counselling Women of Drug, Chemical, and Radiation Exposure During the First Trimester*", (1990)⁴, Koren showed that pregnant women exposed to drugs that are known to be non teratogenic, still perceive that their born-to-be baby has a 24 % chance to suffer a major birth defect. This is about the same risk as an intra-uterine exposure to Thalidomide.
- 15 [0011] Scientific studies aimed at measuring the risk of drugs during pregnancy and patient education and counseling have so far been at the forefront of efforts to achieve better patient compliance with medical prescription.

- [0012] However, even in the case of drugs having an extensively demonstrated record of fetal innocuousness, such as Diclectin® used to curb nausea and vomiting, the perception of latent risk remains. This perception of risk is of course carried over from the negative experiences of thalidomide which was also prescribed for nausea and vomiting during pregnancy and which was also provided as an oral dosage form. However, in reality, the active ingredient thalidomide and the active ingredients of Diclectin®, namely pyridoxine HCl and doxylamine succinate are completely unrelated. The risk perception carried-over from thalidomide is made apparent from patient compliance inquiries. Patient compliance with a medically prescribed dosage regimen of Diclectin® is clearly below what is recommend in the medical profession.

[0013] Even physicians and pharmacists are anxious about their liability associated with prescription or dispensing of medications to pregnant women. In the study by Pole⁵, it was shown that even health care professionals, after reading four different labels (all of them stating that drug is safe to be used in pregnancy), 5 have evaluated these labels, as bearing a residual risk. They were unable to fully perceive or accept that medication is safe to be used in pregnancy. Patients, physicians and pharmacists are also worried about erroneous ingestion or dispensing of drugs not intended for use during pregnancy.

[0014] Despite the enormous volume of scientific evidence supporting 10 Diclectin® harmlessness to the fetus, pregnant women persistently do not follow their physician's recommendation as to the adherence to Diclectin® dosage regimen. In most cases, women voluntarily reduce the dosage by half. In fact, they do not comply with the proper dosage regimen for Diclectin® to the point that some woman and some physicians believe that the medication is not effective. 15 Therefore, non-compliance often results in a perception of product effectiveness failure.

[0015] Due to non-compliance with medical prescription, patients using less than prescribed amounts of Diclectin® will often find themselves in sub-therapeutic state. This prevents the medication from being effective and may 20 aggravate the mother's condition to the point of developing hyperemesis gravidarum (HG). HG is the most severe end of nausea and vomiting during pregnancy, when a pregnant woman suffers from loss of more than 5% of her pre-pregnancy body weight, dehydration, acid-base disturbances, ketonuria and electrolyte imbalance. At this stage, physicians use intravenous medications that 25 are often not recognised for safe use during pregnancy in order to control maternal condition. The use of these medications poses an unnecessary risk to the fetus. If this last resort medication appears to be ineffective due to the deterioration of the woman's condition, a therapeutic abortion may even be considered⁶.

[0016] In order to diminish potential for birth defects a vitamin intake is now medically recommended during pregnancy. For example, clinical evidence shows that taking folic acid before conception and during the first trimester of pregnancy may prevent up to 72% of the congenital abnormalities spina bifida and
5 anencephaly⁷. Despite this, pregnant women are generally non compliant with recommended folic acid intake treatment thus putting an unborn child at an increased risk of major birth defect.

[0017] The situation is even worse if pregnant woman has been on a drug therapy that interferes with folic acid receptors (e.g., phenobarbital, phenytoin,
10 carbamazepine, valproic acid). In this case, a pregnant woman is even at greater risk for having a baby with birth defect if she is not compliant.

[0018] Thus there remains an important need for innovative solutions to achieve better patient compliance of vitamins or drugs recommended for use during pregnancy.

15 **OBJECTS OF THE INVENTION**

[0019] An object of the present invention is therefore to provide an improved oral dosage form for, *inter alia*, achieving better patient compliance with vitamins or drugs intended for use during pregnancy.

[0020] Another object is to provide a method for improving patient
20 compliance of pregnant women by diminishing their perception of teratogenic risk and by direct implication to improve product effectiveness of dosage forms containing at least one active ingredient and intended for use by pregnant women.

[0021] A further object is to provide a method for diminishing the incidence
25 of erroneous ingestion by pregnant women or of erroneous dispensing by pharmacists of therapeutic agents not prescribed to said pregnant women.

SUMMARY OF THE INVENTION

[0022] More specifically, in accordance with the present invention, there is provided a pharmaceutical dosage form comprising at least one active ingredient, such as for example a vitamin supplement or a synergistic combination of 5 pyridoxine HCl and doxylamine succinate, and destined for administration to pregnant women, the pharmaceutical dosage form bearing pregnancy-friendly indicia. In a preferred embodiment the pregnancy-friendly indicia is in the shape of a graphical illustration of a pregnant woman applied to the dosage form itself or to its packaging. In a most preferred embodiment, the dosage form is destined for 10 oral administration.

[0023] Also provided is a method of diminishing the perception of teratogenic risk among pregnant women taking a pharmaceutical dosage form containing at least one active ingredient. The method comprising providing said pharmaceutical dosage form bearing pregnancy-friendly indicia, preferably in the 15 shape of a graphical illustration of a pregnant woman applied to the dosage form itself or to its packaging.

[0024] Also provided is a method of improving patient compliance of pregnant women with medically recommended dosage regimen of at least one active ingredient. The method comprising providing a pharmaceutical dosage form 20 bearing pregnancy-friendly indicia. Improving patient compliance also leads to improved product effectiveness because product effectiveness is linked to patient compliance. Thus, the method of the present invention also leads to improved product effectiveness.

[0025] Also provided is method of diminishing the incidence of erroneous 25 ingestion by pregnant women or of erroneous dispensing by pharmacists of therapeutic agents not prescribed to said pregnant women. The method comprising providing a pharmaceutical dosage form comprising at least one active ingredient prescribed to said pregnant women, the dosage form bearing

pregnancy-friendly indicia apt to graphically distinguish dosage forms intended to be used during pregnancy from others.

[0026] Other objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of 5 preferred embodiments thereof, given by way of example only with reference to the accompanying drawing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] Figure 1 is a pictorial representation of an improved oral dosage form in accordance with the present invention and bearing a visible indicia apt to 10 achieve improved patient compliance.

DESCRIPTION OF THE PREFERRED EMBODIMENT

[0028] The main object of the present invention is therefore to provide an improved oral dosage form for achieving better patient compliance with drugs prescribed for use during pregnancy. This objective is surprisingly and effectively 15 achieved by applying pregnancy-friendly indicia on the dosage form. Dosage form is understood to encompass its packaging. By "pregnancy-friendly" indicia is meant any graphical or textual representation apt to be easily recognized as indicative of a safe medication for taking during pregnancy.

[0029] In a most preferred embodiment, the pregnancy-friendly indicia are a 20 graphical representation of the profile of a pregnant woman having a hand resting on her stomach region. Such graphical representation is illustrated in Figure 1 and has a particularly comforting effect on expectant mothers and have been statistically shown to substantially lower the perception of teratogenic risk and consequently lead to elevated patient compliance. Such evidence is presented in 25 the examples provided below.

Example 1

[0030] A study was conducted with 12 pregnant women. This study was aimed at testing if pregnancy-friendly indicia such as the indicia illustrated in Figure 1 may have a positive impact by reducing the perception of teratogenic risk of a drug taken during pregnancy, and if it is the case, which kind of design is most effective in improving patient compliance.

5 [0031] Different designs of pregnancy-friendly indicia were printed on tablets. This aim was to ascertain if, when used, those indicia would increase the patients' confidence in taking the tablet during pregnancy by reducing the 10 perception of teratogenic risk. Diminishing the perception of teratogenic risk would consequently improve patient compliance and as a result achieve better treatment effectiveness.

15 [0032] The study revealed while all pregnancy-friendly indicia are helpful at diminishing the perception of teratogenic risk, the most preferred graphical representation is that of Figure 1. The graphical representation shown in Figure 1 would indicate in a clear and precise fashion that the medication has been specifically designed for the pregnant woman.

20 [0033] This surprising positive effect on patient compliance would of course translate itself in the effectiveness of a vitamin or drug treatment and a concurrent reduction of medical complications for the pregnant woman and the fetus.

Example 2

25 [0034] To further validate the findings disclosed in Example 1, an observational, prospective survey on pregnant women in family practice offices and obstetrician offices was conducted. The statistical tool used for measuring the objective of the study (how reassured about fetal safety woman feels taking one or the other tablet once prescribed to them) was a validated scientific tool for

subjective measurements: a visual analog scale (VAS) from 1-5 (1 being the least safe and 5 being the most safe). Patients were told that the prescribed drug, in tablet form, was safe for use in pregnancy and were asked to label on the VAS how reassured about fetal safety they felt when taking the tablet. They were shown
 5 two different tablets, one plain white and the other white with the illustration of Figure 1 applied to the tablet.

[0035] Data was collected from 132 pregnant women and the results are shown in the table below:

Test: Dual-Sample Assuming Equal Variances

- 10 **Teratogenic Risk Perception on Scale of 1 to 5 with 1 being greatest risk perception.**

	Plain White tablet	Tablet with pregnancy-friendly indicia as per Figure 1
Observations	132	132
Mean Risk Perception	2,5227	3,6969
Variance	1,2132	1,3120
P($T \leq t$) one-tail		P< 0.0001

[0036] The study clearly showed superiority of the tablet with a printed pregnant woman concerning the perception of the teratogenic risk (results were
 15 statistically significant with P<0.0001). The P value of 0.0001 signifies that the result of this study as 1/10,000 chance to be the result of chance only. If we repeat this study 10,000 times, in 9,999 cases, the same results would be obtained. Usually P<0.05 is recognized as medically significant.

[0037] Thus, in the sample group of 132 pregnant women, 23.4% felt more reassured about the fetal safety of taking the tablet with a printed pregnant woman as shown in Figure 1, than a plain white tablet.

[0038] Of course, these results would translate themselves directly into
5 improved patient compliance by a margin of at least 23.4%. Thus, a strong conclusion emerges that the presence of pregnancy-friendly indicia on a vitamin or drug to be taken during pregnancy will significantly reduce teratogenic risk perception and by the same token improve patient compliance with prescribed dosage regimen.

10 [0039] Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims. More specifically, the exact appearance of pregnancy-friendly indicia is variable with the understanding that some indicia will induce greater patient compliance
15 than others. Also, it is to be understood that although examples were given in relation to oral tablets, other pharmaceutical dosages forms are of course covered by the present invention. Thus, pregnancy-friendly indicia may appear on the actual dosage form, such as tablet, sugar coated tablet, sublingual tablet, caplet, capsule, gel capsule, chewable tab, pill, suppository, powder, vial, ampoule, pre-
20 filled syringe, nasal spray, pastille, syrup, drops, vaginal ovule, subcutaneous implant, transdermal gel, transdermal patch, transmucausal strip, pouch, or may also appear on the packaging and labeling of the dosage form.

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